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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,839	LAMBETH ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,10-17,26 and 27* is/are pending in the application.

4a) Of the above claim(s) *27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,10-17 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Examiner of Record is now Thaian N. Ton of Art Unit 1632.

Applicants' Amendment, filed 11/22/04, has been entered. Claims 2, 5, 7-9, and 18-25 have been cancelled. Claims 1, 3, 4, 6, 10-17 and 26 have been amended. Claim 27 has been added. Claims 1, 3, 4, 6, 10-17, 26 and 27 are pending. Claim 27 is withdrawn. Claims 1, 3, 4, 6, 10-17 and 26 are under current examination.

Election/Restrictions

Newly submitted claim 27 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Claim 27, as amended, recites that the transgenic mouse of claim 1 is a multiple intestinal neoplasia (Min) mouse. The invention claimed in claim 27 is found to be unrelated to the invention as originally claimed, which is a transgenic mouse, the nucleated cells of which comprise a transgene encoding Nox1, wherein the transgene comprises a nucleic acid sequence set forth as SEQ I DNO: 1, or a degenerate variant thereof, operably linked to a promoter, and wherein the mouse exhibits an increased overgrowth of colonic epithelial cells upon exposure to pathogenic bacteria. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the

instant case the different inventions the Min mouse of claim 27 is structurally and functionally different than the mouse as claimed in claim 1.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 27 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 101

The prior rejection of claims 1, 3, 4, 6, 10-17 is withdrawn in view of Applicants' arguments, particularly, that the mice disclosed in the instant specification, when heterozygous for a transgene encoding NOX1 have an increased hyperplastic response in the colon in response to a pathogenic bacteria, as compared to wild-type mice. See Examples 10, 11 of the specification and p. 7 of the Response.

Claim Rejections - 35 USC § 112

The prior rejection of claims 1-6 and 9-18, for written description, as advanced on pages 16-21 of the prior Office action is withdrawn in view of Applicants' amendment to recite that SEQ ID NO: 1 encodes NOX1 and clarification as to the phenotype of the claimed transgenic mice.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 6, 10-17 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The claims are directed to a transgenic mouse, the nucleated cells of which comprise a transgene encoding NOX1, wherein the transgene comprises a nucleic acid sequence set forth as SEQ ID NO: 1 or a degenerate variant thereof, operatively linked to a promoter, and wherein the mouse exhibits an increased overgrowth of colonic epithelial cells upon exposure to pathogenic bacteria. In further embodiments, the claims are directed methods of using the mice for identifying a therapeutic agent for use in treating inflammation or colon cancer and cells isolated from the mouse.

The instant disclosure fails to adequately describe the specific embodiment of a *degenerate variant* of SEQ ID NO: 1 as to reasonably convey to one skilled in the

relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. Although the instant specification provides sufficient description of SEQ ID NO: 1, the specification does not provide sufficient description or support for degenerate variants of SEQ ID NO: 1. A careful review of the description fails to provide specific support for such degenerate variants. The claimed invention as a whole is not adequately described if the claims require essential or critical elements that are not adequately described in the specification, and which are not conventional in the art, as of Applicants' effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient, relevant identifying characteristics (as it relates to the invention as a whole), such that one of skill in the art would recognize that Applicants had possession of the claimed invention. In the instant case, the claimed embodiments of *degenerate variants* of SEQ ID NO: 1 lack a written description. The specification fails to provide any description of degenerate variants of SEQ ID NO: 1. Furthermore, the skilled artisan could not envision such degenerate variants, encompassed by the claims, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method.

Furthermore, the specification fails to provide an adequate description of the claimed embodiments of methods of utilizing the claimed transgenic mice for identifying a therapeutic agent for use in the treatment of inflammation or colon

cancer, as newly amended. See claims 15 and claims dependent therefrom. In particular, the specification fails to provide sufficient description with regard to the exposure of the NOX1 transgenic mouse to a pathogenic bacteria, such that the mouse exhibits an increased overgrowth of colonic epithelial cells when compared to a wild-type mouse, and then utilizing this mouse for identifying therapeutic agents for the treatment of colon cancer or inflammation. There is no description in the specification with regard to inflammation or colon cancer in the claimed mice, merely the description that the mice have increased colon crypt depth. Thus, the skilled artisan could not envision utilizing the claimed transgenic mice for the specifically claimed methods.

Adequate written description requires more than a mere statement that it is part of the invention, and a reference to a potential method of isolating it. See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (Fed. Cir. 1991). For example, the instant specification fails to provide any description as to how degenerate a variant would be in order to be considered a degenerate variant of SEQ ID NO: 1. If Applicants feel that description for the term *degenerate variants* of SEQ ID NO: 1 is supported by the filed application, Applicants are invited to point to specific page and line number as to where this support can be found.

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 6, 10-17 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a transgene encoding NOX1, as set forth in SEQ ID NO: 1, operatively linked to the CX1 promoter, wherein the mouse exhibits an increased overgrowth of colonic epithelial cells upon exposure to pathogenic bacteria, and cells isolated from the transgenic mice, the specification does not reasonably provide enablement for the breadth of the claimed invention, encompassing a transgenic mouse, the nucleated cells of which comprise a transgene encoding Nox1, wherein the transgene comprises a nucleic acid sequence set forth as SEQ ID NO: 1 or a degenerate variant thereof, operatively linked to any promoter, wherein the mouse exhibits an increased overgrowth of colonic epithelial cells upon exposure to pathogenic bacteria, and methods of using the claimed mice to identify therapeutic agents for use in treating inflammation or colon cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors

have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants argue that with regard to the prior Office action, that the NOX1 transgenic mice, as instantly claimed, have a phenotype – an increased hyperplastic response in the colon in response to pathogenic bacteria as compared to wild-type mice, and that these mice and cells isolated therefrom are useful in identifying agents for treating proliferative disorders, such as colon cancer, and thus, the instantly claimed mice are fully enabled by the specification. See pp. 9-10 of the Response. Applicants further argue that the prior rejection, which alleges that the claimed methods of utilizing the claimed transgenic mice are not enabled by the specification, as no phenotype is provide, is based upon the erroneous assumption that the NOX1 mice do not have a phenotype. Applicants argue that the hyperplastic response found in the NOX1 mice is found to be significantly increased when compared to wild-type animals. Applicants argue that this data shows the phenotype in mice expressing NOX1. See p. 12 of the Response. Applicants argue that the claimed transgenic mice exhibit an increased overgrowth of colonic epithelial cells upon exposure to pathogenic bacteria and that these mice can be used to identify agents capable of treating proliferative disorders, such as colon cancer. Applicants argue that there is no data with regard to the NOX1/Min mice in Figure 4, and that Figure 4 represents the phenotype of the NOX1 mice. See p. 13 of the Response.

This is found to be partially persuasive. It is acknowledged that the claimed NOX1 transgenic mice have the phenotype of increased overgrowth of colonic epithelial cells in response to pathogenic bacteria, when compared to wild-type mice, as evidenced by Example 11 of the instant specification. However, the breadth of the methods of using the instantly claimed mice is not found to be enabling. Applicants point to the specification (p. 23, line 3 to page 25, line 21) for support for enabled uses for the claimed mice. The claims are directed to using the claimed transgenic mice for identifying therapeutic agents for use in treating inflammation or colon cancer. The mice of the instant invention show a phenotype of increased overgrowth of colonic epithelial cells (as evidenced by increased colon crypt depth) when exposed to a pathogenic bacteria. The specification does not provide any nexus between this observed phenotype and colon cancer or inflammation, as instantly claimed. There is no specific teachings or guidance with regard to the increased colon crypt depth and the onset of cancer. Furthermore, there is no teaching or guidance provided by the specification with regard to increased colon crypt depth and inflammation. It is noted, as previously, that inflammation is a multi-faceted disease (see pp. 15-16), and the claims are directed to general inflammation. However, the mice of the claimed invention do not have inflammation, and further, the specification only teaches analysis of the colon of these mice. Absent a nexus between the observed phenotypes of increased colon crypt depth and overgrowth of colonic epithelial cells, and inflammation or colon

cancer, it would have required undue experimentation for one of skill to practice the claimed methods, using the claimed mice.

With regard to the promoter used, Applicants submit that the production of transgenic mice, and the use of any promoter, is enabled by the specification. Applicants argue that expression vectors for the production of transgenic mice and promoters of use are described in the specification, and one of skill in the art can readily identify promoters of use. Applicants present Exhibit A as evidence to show a list of promoters known to be used in the creation of transgenic models, and Exhibit B, which is a list of promoters that have been used to create a single coding sequence. See p. 10, 1st ¶, and p. 11-12, of the Response.

This is not found to be persuasive. The specification teaches that the transgenic mice of the instant invention comprise a transgene encoding NOX1 (SEQ ID NO: 1) that is operably linked to the CX1 promoter. These mice have a particular phenotype, that they exhibit overgrowth of colonic epithelial cells upon exposure to pathogenic bacteria. Although Applicants point to the specification and Exhibits A-B for support that any particular promoter would work as instantly claimed, it is noted that, as stated in the previous Office action (see p. 10, last ¶) that the specification provides no guidance as to using any promoter to produce the claimed animal, because the promoter used must be able to express in the appropriate cell type, in the appropriate location (in the instant case, the colon) with sufficient levels of expression, to result in the claimed phenotype of an

increased overgrowth of colonic epithelial cells upon exposure to pathogenic bacteria. Although the Exhibits presented by Applicants provide teachings with regard to utilizing specific promoters to produce specific transgenic mice with specific phenotypes, these teachings are not sufficient to overcome the art-recognized unpredictability in the generation of transgenic animals, particularly in the resulting phenotype (see also, prior Office action, pp. 9-12). Thus, absent specific teachings with regard to the breadth of the claims utilizing any promoter to drive the expression of NOX1, and in view of the art with regard to the unpredictability of the resulting phenotype of a transgenic mouse, it would have required undue experimentation for one of skill in the art to make and use the claimed mouse.

Applicants point to the citation of Capecchi *et al.* to support that the potential now exists to generate mice of any desired genotype, and thus, the Office provides an admission that one of skill in the art can readily generated transgenic mice including any gene of interest. See p. 10, last ¶ of the Response.

This is not found to be persuasive. The citation of Capecchi *et al.* does teach that mice of any desired genotype can be generated. However, the unpredictability of the generation of transgenic mice lies in the resulting phenotype. The prior Office action provides evidence that this is true in generation of transgenic non-human mammals. The art supports that even mice, the resulting phenotype of a transgenic mouse cannot be reasonably predicted. Note that the mere capability to

perform gene transfer in a mouse is not enabling because a desired phenotype cannot be predictably achieved by simply introducing transgene constructs. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends upon the particular gene construct used, to an unpredictable extent. Accordingly, it would have required undue experimentation for one of skill in the art to make and use the claimed NOX1 transgenic mice.

Claim Rejections - 35 USC § 112

The prior rejection of claim 15, as indefinite, with regard to the term "inflammation" is withdrawn in view of Applicants' arguments.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 4, 6, 10-17 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites that the *nucleated cells* of the mouse comprise a transgene encoding NOX1. This is unclear, because the metes and bounds of "nucleated cells" is not specifically defined by the specification. For example, nucleated cells can refer to some or all of the cells of the mouse. Further, nucleated cells could refer to

cells that are added to the mouse. Appropriate correction or clarification is requested. Claims 3, 4, 6, 10-17 and 26 depend from claim 1.

Claim Rejections - 35 USC § 103

The prior rejection of claims 1-6 and 9 as being obvious over Suh in view of Capecchi, and the prior rejection of claims 1-4 and 9 over Dupuy in view of Capecchi, is withdrawn in view of Applicants' amendment to the claims, reciting the specific phenotype of the claimed NOX1 transgenic mice.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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